2. RESPONSE/REMARKS

2.1 STATUS OF THE CLAIMS:

Claims 1-4, 6-8, 10-16, 19-20, 22-24, 28, 30, 32, 33, 43-45 and 47 were pending at the time of the Action, and subject to a restriction requirement.

Claims 1, 10-15, 30, 32, 33, 43, 45, and 47 (directed to provisionally non-elected inventions), are canceled herein without disclaimer.

Claims 2-4, 6-8, 16, 19-20, 22-24, 28, and 44 have been amended herein.

Claims 52-60 have been added herein.

Claims 2-4, 6-8, 16, 19-20, 22-24, 28, 44, and 52-60 are now pending in the application.

2.2 SUPPORT FOR THE AMENDMENT:

The pending claims are fully supported by the original specification and claims as filed. It is Applicants' belief that no new matter is included by entry of the present paper.

2.3 UNITY OF INVENTION UNDER TREATY RULE 13.1:

PCT Rule 13.1 provides that in a national-stage application it is permissible to examine "(i) in addition to an independent claim for a given product, an independent claim for a process specially adapted for the manufacture of said product, and an independent claim for a use of the said product." Stated differently, Unity of Invention is maintained in an application where claims are directed to (a) a process for manufacturing a product; (b) a method of using the product, and (c) the product itself.

The Office considers on page 2 of the Action, however, that the claims in the present application lack Unity of Invention under this rule.

Applicants respectfully traverse, and point out that pending claims are directed to a product, and to methods of using the product both *in vivo,* and *in vitro.* As such, the pending claims define a "unified" invention under *PCT Rule 13.1*, and with all due respect the present finding of lack of unity is therefore improper because this is a national stage application of PCT/US2003/012225.

2.3.1 THE CRITERIA FOR UNITY OF INVENTION UNDER PCT RULE 13 IS CLEAR.

PCT Rule 13 states in pertinent part:

> *"The international application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention").*
>
> *Where a group of inventions is claimed in one and the same international application, the requirement of unity of invention referred to in* Rule 13.1 *shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.*
>
> *The determination whether a group of inventions is so linked as to form a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives within a single claim.*
>
> *Subject to* Rule 13.1, *it shall be permitted to include in the same international application a reasonable number of dependent claims, claiming specific forms of the invention claimed in an independent claim, even where the features of any dependent claim could be considered as constituting in themselves an invention."*

2.3.2 UNITY OF INVENTION UNDER PCT RULE 13 IS SUPPORTED BY 37 C.F.R. § 1.475.

37 C.F.R. §1.475 states in relevant part:

> *(a) An international and a national stage application shall relate to one invention only or to a group of inventions so linked as to form a single general inventive concept ("requirement of unity of invention"). Where a group of inventions is claimed in an application, the requirement of unity of invention shall be fulfilled only when there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. The expression "special technical features" shall mean those technical features that define a contribution which each of the claimed inventions, considered as a whole, makes over the prior art.*
>
> *(b) An international or a national stage application containing claims to different categories of invention will be considered to have unity of invention if the claims are drawn only to one of the following combinations of categories:*
>
> *(1) A product and a process specially adapted for the manufacture of said product; or*
>
> *(2) A product and a process of use of said product; or*
>
> *(3) A product, a process specially adapted for the manufacture of the said product, and a use of the said product; or*
>
> *(4) A process and an apparatus or means specifically designed for carrying out the said process; or*
>
> *(5) A product, a process specially adapted for the manufacture of the said product, and an apparatus or means specifically designed for carrying out the said process.*

Interpreting the requirements of *Rule 13.1*, the *M.P.E.P.* provides clear and exhaustive guidance to Examiners in the Office regarding the means for determining when a lack of unity of invention may be found under *Rule 13.1* and *Rule 13.2*. The *Manual* in Chapter 1850 (part II) states in pertinent part:

> *"Although lack of unity of invention should certainly be raised in clear cases, it should neither be raised nor maintained on the basis of a narrow, literal or academic approach. There should be a broad, practical consideration of the degree of interdependence of the alternatives presented, in relation to the state of the art as revealed by the international search or, in accordance with* PCT Article 33(6), *by any additional document considered to be relevant.*
>
> *If the common matter of the independent claims is well known and the remaining subject matter of each claim differs from that of the others without there being any unifying novel inventive concept common to all, then clearly there is lack of unity of invention. If, on the other hand, there is a single general inventive concept*

that appears novel and involves inventive step, then there is unity of invention and an objection of lack of unity does not arise.

For determining the action to be taken by the examiner between these two extremes, rigid rules cannot be given and each case should be considered on its merits, the benefit of any doubt being given to the applicant" (emphasis added).

The *Manual* further states:

*Unity of invention has to be considered in the first place only in relation to the independent claims in an international application and not the dependent claims. By "dependent" claim is meant a claim which contains all the features of one or more other claims and contains a reference, preferably at the beginning, to the other claim or claims and then states the additional features claimed (*PCT Rule 6.4*). The examiner should bear in mind that a claim may also contain a reference to another claim even if it is not a dependent claim as defined in* PCT Rule 6.4. *One example of this is a claim referring to a claim of a different category (for example, Apparatus for carrying out the process of Claim 1 ...," or "Process for the manufacture of the product of Claim 1 ..."). Similarly, a claim to one part referring to another cooperating part, for example, "plug for cooperation with the socket of Claim 1 ...") is not a dependent claim.*

If the independent claims avoid the prior art and satisfy the requirement of unity of invention, no problem of lack of unity arises in respect of any claims that depend on the independent claims. In particular, it does not matter if a dependent claim itself contains a further invention." Ibid. (emphases added).

2.3.3 REQUIREMENT FOR RESTRICTION:

The Office has taken the position that the pending claims are drawn to four inventions that are allegedly not linked so as to form a single general inventive concept under *Rule 13.1*. The Action on page 2 states that the Application allegedly contains claims directed to four distinct inventions. As such the Office has issued a requirement for restriction. The four allegedly-distinct inventions are exemplified by the following groups:

***Group I** - Claims 1-4, 6-8, 10-16, 19, 20, 22-24, 28, 30, 32, 33 and 43, drawn to an adeno-associated viral (AAV) vector or an AAV virus comprising a first nucleic acid encoding an AAV capsid protein having an exogenous amino acid sequence that*

binds to a mammalian lipoprotein receptor, LDL receptor or VLDL receptor, or said exogenous amino acid sequence comprises the sequence of any one of SEQ ID NO:1-20 and 22-31, or further comprises a second nucleic acid encoding an expressed therapeutic agent, a mammalian cell comprising said vector, and a kit comprising said vector and instructions for using said kit;

Group II *- Claim 44, drawn to a method for targeting an AAV virion or viral particle to a mammalian cell comprising a cell-surface lipoprotein receptor by providing to a population of cells an AAV virion or viral particle comprising said vector;*

Group III *- Claim 45, drawn to a method for targeting an expressed therapeutic agent to a mammalian cell comprising a cell-surface lipoprotein receptor by providing a mammal the AAV expression system of claim 8; and*

Group IV *- Claim 47, drawn to a method for preventing, treating or ameliorating the symptoms of a disease, dysfunction, or deficiency in a mammal comprising administering to said mammal the virion of claim 30 or the plurality of AAV viral particles of claim 32.*

Despite the plain language of *Rule 13.1*, the Regulations set forth in *37 C.F.R. § 1.475*, and the copious explanation provided in Section 1850 (I) and (II) of the *Manual* (*supra*), the Office asserts on page 2 of the present Action, however, that the original claims in the application lack unity of invention under this Treaty rule. Applicants respectfully assert that there is no lack of unity of invention, as the pending claims are drawn to a product, and to methods for their use (both *in vivo*, and *in vitro*). As such Applicants respectfully request that the restriction requirement be vacated.

In the alternative, and to be fully responsive to the Action, Applicants hereby provisionally elect, ***with traverse***, to prosecute the subject matter of the **Group II** invention, should the requirement for restriction be made final. Applicants note that all pending claims read on the **Group II** invention.

2.3.4 THE "FURTHER RESTRICTION" IS IMPROPER.

In addition to the purported lack of unity with respect to the four groups of claims summarized above, the Office looks to claim 4 as justification for finding a *further* lack of unity, simply because the dependent claims recite an element that comprises at least one amino acid sequence from within a proper Markush group. The Action at page 3, 1st paragraph, indicates that "(u)pon election of any of group I-IV, further restriction is required. Applicant is required to select one SEQ ID No. The sequences of SEQ ID Nos.1-20 and 22-31 represent nucleotide sequence (*sic*) encoding different peptides or proteins that have different structures, biological functions and different usages. They require separate (*sic*) search and the search would not be coextensive. Thus the sequences of SEQ ID Nos. 1-20 and 22-31 are patentably distinct from each other. It is noted that this is a restriction and NOT an election of species." (Emphasis in original).

Applicants respectfully traverse and object to this "further restriction." First, contrary to the Office's position, **none** of the sequences recited in SEQ ID NO:1 to SEQ ID NO:20 and SEQ ID NO:22 to SEQ ID NO:31 are *nucleotide* sequences. Each of the disclosed sequences represents the primary amino acid sequence of an ApoE or ApoE-homologous peptide, or a consensus sequence thereof. Therefore, the characterization of these sequences as distinctly different *polynucleotides* is incorrect. Even a cursory review of the Specification and the Sequence Listing itself would provide ample evidence that the recited sequences are highly-conserved ApoE-derived peptides.

Moreover, Section 6 of the Specification details the origin of the individual peptide species, as well as provides consensus sequences that encompass the individual species of peptides. If each member of a group of peptides can be aligned at the primary amino acid level to produce a consensus peptide sequence, then the individual sequences *by definition* must be species of a genus. For that

additional reason alone, the "further restriction" is clearly improper, and Applicants respectfully request that it be withdrawn, or at least be re-issued as an *election of species*, and not a "further restriction."

2.3.5 Reliance upon a Single Dependent Claim for Determination of Unity of Invention is Improper.

Reliance upon elements of the Markush group of dependent claims 4, 6-7, or 11-13; however, is a direct contravention of the Patent Cooperation Treaty directive that "[u]nity of invention has to be considered in the first place only in relation to the independent claims in an international application and not the dependent claims."

Again, all of the recited elements comprise *species* of the claimed invention, and by definition cannot be four patentably-distinct inventions as the Office has asserted.

2.3.6 The Holding that a Search of More than One Sequence Represents an Undue Burden for the Office is Both Arbitrary and Capricious.

The Action at page 3 states that in order to conduct an examination of the claims, a "separate search" would be required and such a search "would not be coextensive." Applicants respectfully traverse, and respectfully note that a search of the small highly-conserved peptides recited in claim 4 would NOT present an undue burden on the Patent and Trademark Office. Further, searching of amino acid sequences against databases of known sequences has been available and routine to the skilled artisan in the molecular biology field for nearly two decades. Moreover, these searches are automated and performed with the aid of computers using well-known and widely-available algorithms and sophisticated search engines. The searching of more than one peptide sequence is not

therefore analogous to searching through shoes and shoes of published patents to find matching sequences. The automatic search process relied on by the Office allows Examiners to submit any number of sequences for electronic search, and such a search is able to scan millions of documents and sequences in a manner of minutes to identify references that teach homologous, related, or identical sequences. That the individual peptides recited in the sequence listing are at most 28 amino acids in length (and many of which are only 13-16 amino acids in length) refutes the notion that their search would be overly burdensome to the Office.

37 C.F.R. has historically provided that "a reasonable number of species" can be searched without undue burden upon the Office. Over the past two decades, the standard that evolved in the chemical arts has also been applied to the recitation of polypeptides and polynucleotides, since; they are in fact chemical entities, albeit ones of *biochemical* origin. One need only examine the thousands of U.S. patents that have issued in the past 15 to 20 years from the same Examining division as that of the present application, to realize that the process of searching a "reasonable number of species" is neither "undue" nor "burdensome." Thus, for the record, the Office's change in this searching is believed to be an arbitrary and capricious one.

Moreover, with respect to polynucleotide species, *M.P.E.P. § 2434* specifically addresses the issue of what constitutes a "reasonable number" of sequences for an examination in the Office.

In pertinent part, the guideline states:

> *The U.S. Patent and Trademark Office published its policy for the examination of patent applications that claim large numbers of nucleotide sequences in the* Official Gazette, 1192 O.G. 68 (November 19, 1996). *Nucleotide sequences encoding different proteins are structurally distinct chemical compounds and are unrelated to one another. These sequences are thus deemed to normally constitute independent and distinct inventions within the meaning of* 35 U.S.C. § 121. *Absent evidence to the contrary, each such nucleotide sequence is presumed to represent an independent and distinct invention, subject to a restriction requirement pursuant to* 35 U.S.C. § 121 *and* 37 C.F.R. § 1.141. ***In establishing the new policy, the***

> ***Commissioner has partially waived the requirements of* 37 C.F.R. § 1.141 *and will permit a reasonable number of such nucleotide sequences to be claimed in a single application. Under this policy, in most cases, up to 10 independent and distinct nucleotide sequences will be examined in a single application without restriction.*** *Those sequences which are patentably indistinct from the sequences selected by the applicant will also be examined. Nucleotide sequences encoding the same protein are not considered to be independent and distinct and will continue to be examined together. In some exceptional cases, the complex nature of the claimed material may necessitate that the reasonable number of sequences to be selected be less than 10." (emphasis added).*

By analogy, Applicants respectfully object to the conclusion that a search of the individual polypeptide species recited in certain dependent claims presented herein (*e.g.*, claims 4, 6-7, and 11-13) would bring an undue burden upon the Office. At a minimum, the Commissioner has determined that as many as 10 nucleotide sequences can be readily examined in a single application without restriction.

If it were the intent of the Congress to permit an Applicant to obtain a patent for only a *single species* of a *single genus*, however, then there would have been no need for the *Statutes* and the *Code* and the courts to permit and to provide for concepts such as Markush language, generic claims, linking claims, rejoinder, election of species, and so on. In fact, the entire discussion of a "species election" would be moot if a patentee were only allowed to present only a single claim to a single example of a single restriction "group."

The very fact that the *Code* specifically provides for the examination of generic and sub-generic inventions, and that the Office has historically had a stated a policy of searching about 10 sequences in a given application, is evidence that there is no "undue burden" on the Office to examine a reasonable number of sequences. Moreover, a contrary decision now would be improper agency action that contravenes the requirements of the *Statutes* and *Code*. Applicants are utterly

perplexed by the "further" restriction advocated in the Action, particularly in view of its apparent contradiction of *years* of examination precedent by the Office even within Technology Center 1600.

Applicants therefore respectfully urge the Office to be consistent in the application of its policies and guidelines, and to permit the searching and examination of more than one sequence in the present application—and as many as ten such sequences. To do otherwise would represent an arbitrary and capricious action that would unfairly injure the Applicants' attempt to obtain patent protection for particular aspects of their invention.

2.4 APPLICANTS' REQUEST RECONSIDERATION OF THE "FURTHER" RESTRICTION.

Applicants formally request that the lack of unity holding be reconsidered, and that the holding of a "further restriction" (for which there appears to be no statutory or other basis) be vacated.

As an alternative, and in an effort to bring about timely examination, Applicants propose that if it is *absolutely* necessary, the "further restriction" could be vacated in view of an election of species from the genus of peptide sequences set forth in the application. If the "further restriction" requirement were vacated, and an election of species requirement made of record, Applicants would accept, *without traverse*, the election provided herein. As evidence of Applicants' willingness to accommodate timely examination, the pending claims have been amended to recite not more than ten ApoE-derived peptides.

To that end, Applicants urge the Office's vacation of the Lack of Unity holding, and vacation of the "further restriction" requirement with respect to the individual peptide species set forth in various dependent claims, and examination on the merits to begin with all pending claims. However,

in view of Applicants' traversal of these holdings, Applicants provisionally elect prosecution of the subject matter of the **Group II** invention with an election of species of a single peptide (*e.g.*, SEQ ID NO:10), to begin prosecution on the merits.

2.5 APPLICANTS REQUEST RECONSIDERATION UNDER 37 C.F.R. § 1.143.

Pursuant to *37 C.F.R. § 1.143*, which states in pertinent part:

> *If the applicant disagrees with the requirement for restriction, he may request reconsideration and withdrawal or modification of the requirement, giving the reasons therefor. In requesting reconsideration the applicant must indicate a provisional election of one invention for prosecution, which invention shall be the one elected in the event the requirement becomes final. The requirement for restriction will be reconsidered on such a request. If the requirement is repeated and made final, the examiner will at the same time act on the claims to the invention elected.*

Applicants also refer to the following pertinent part of *M.P.E.P. § 806.04*:

> *Where an application includes claims directed to different embodiments or species that could fall within the scope of a generic claim, restriction between the species may be proper if the species are independent or distinct. However, 37 C.F.R. § 1.141 provides that an allowable generic claim may link a reasonable number of species embraced thereby.*

The practice is also set forth in *37 C.F.R. § 1.146*, which reads in pertinent part:

> *In the first action on an application containing a generic claim to a generic invention (genus) and claims to more than one patentably distinct species embraced thereby, the examiner may require the applicant in the reply to that action to elect a species of his or her invention to which his or her claim will be restricted if no claim to the genus is found to be allowable. However, if such application contains claims directed to more than a reasonable number of species, the examiner may require restriction of the claims to not more than a reasonable number of species before taking further action in the application.*

2.6 APPLICANTS GIVE CONSTRUCTIVE NOTICE OF THEIR RIGHT TO PETITION

THE "FURTHER RESTRICTION" UNDER 37 C.F.R. § 1.144.

Should a final requirement for "further restriction" from among the peptides recited in dependent claims 4, 6-7, and 11-13 be entered in the present case despite Applicants' arguments against the same, their request for vacation of further restriction and imposition of species election, and the formal request herein for Reconsideration, Applicants hereby give constructive notice of their right to petition the final holding of restriction to the Group Director pursuant to *37 C.F.R. § 1.144*. As provided by the Rule, Applicants currently defer petition until after final action or allowance of the claims provisionally elected.

2.7 APPLICANTS' PROVISIONAL ELECTION OF A SINGLE PEPTIDE SPECIES.

In an effort to comply with both the spirit of the Action, and in order to facilitate initial search and examination of the species encompassed by the elected restriction group, and further in an effort to ensure that subsequent examination of the case is not unduly delayed due to the perceived inaccuracies of the present "further restriction" provision, Applicants' offer a voluntary species election to logically facilitate an expedient prosecution that balances the rights of the Applicants with the examination burden on the Office.

As noted above, Applicants have endeavored to comply with the spirit of the Action by reducing the number of species to a "reasonable number" using the guidelines as set forth in *M.P.E.P. § 2434*, and requesting that a total of ten ApoE-related peptide species be considered, each in succession, beginning with the consensus peptide set forth in **SEQ ID NO:10**, if allowable subject matter is identified upon consideration of the initial species election herein.

To further illustrate the merits of such an election of species, Applicants note that the first

eight peptide species are substantially homologous peptides that they may be readily characterized at the generic (**SEQ ID NO:10**) and sub-generic (SEQ ID NO:9) level to provide two consensus sequences of differing scope:

SHLRKLRKRLLRD (SEQ ID NO:1)

SHLRKLRERLLRD (SEQ ID NO:2)

SHLRKMRKRLLRD (SEQ ID NO:3)

SHLRKLPKRLLRD (SEQ ID NO:4)

SHLRKLRQRLLRD (SEQ ID NO:5)

SHMRKLRKRVLRD (SEQ ID NO:6)

SHLRKMRKRLMRD (SEQ ID NO:7)

SHLRRLRRRLLRD (SEQ ID NO:8)

Sub-Generic ApoE Consensus Sequence:

$SHX_1RX_2X_3X_4X_5RX_6X_7RD$ (SEQ ID NO:9), where X_1 = Leu or Met; X_2 = Lys or Arg; X_3 = Leu or Met; X_4 = Arg or Pro; X_5 = Lys Glu, Gln or Arg; X_6 = Leu or Val; and X_7 = Leu or Met

Generic ApoE Consensus Sequence:

SHXRXXXXRXXRD (**SEQ ID NO:10**) where X = any amino acid

2.8 APPLICANTS PROVISIONALLY ELECT A SINGLE PEPTIDE SPECIES.

Applicants provisionally elect to prosecute, ***with traverse***[1], the ApoE-derived consensus amino acid sequence set forth in **SEQ ID NO:10**.

[1]If the "further restriction" of the individual sequences is withdrawn, and an election of species is entered, Applicants provisional election of a single species would be made ***without traverse***.

2.9 REQUEST FOR EXAMINER/PRACTICE SPECIALIST INTERVIEW

Should the requirement for "further restriction" be maintained and made final with respect to the peptide species recited in the cited dependent claims, Applicants hereby request an interview with the Examiner and a TC1600 Practice Specialist (or Supervisory Patent Examiner) ***before the issuance of a first Office Action on the merits*** to specifically resolve the "further" restriction imposed upon Applicants.

2.10 CONCLUSION

In conclusion, in light of the foregoing remarks, Applicants believe this to be a complete response to the Action, and favorable consideration of the pending claims is therefore respectfully requested. Applicants also expressly reserve their right to file one or more continuation and/or divisional application(s) directed to any non-elected invention(s) and non-elected species at any time during the pendancy of the pending application, or from any application subsequently claiming priority to the present application.

Should the Examiner have any questions, a telephone call to the undersigned Applicants' representative would be appreciated.

Respectfully submitted,

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H-778401v1

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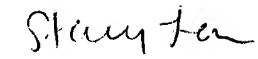

Stacy Lanier